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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/669,187	09/25/2000	Arthur M. Krieg	C1039/7035 (HCL/MAT)	2999

7590 01/13/2006

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EXAMINER

BLANCHARD, DAVID J

ART UNIT

PAPER NUMBER

1643

DATE MAILED: 01/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/669,187

Applicant(s)

KRIEG ET AL.

Examiner

David J. Blanchard

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 October 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,5,15-37,52-54,77,85,88-90,93,98 and 107-120 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,5,15-37,52-54,77,85,88-90,93,98 and 107-120 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 6/27/05.
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____.

DETAILED ACTION

1. Claims 2-4, 6-14, 38-51, 55-76, 78-84, 86-87, 91-92, 94-97 and 99-106 are cancelled.

Claims 1, 5, 77, 107-108 and 112 have been amended.

Claims 113-120 have been added.

2. Claims 1, 5, 15-37, 52-54, 77, 85, 88-90, 93, 98 and 107-120 are pending and under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. This Office Action contains New Grounds of Rejections.

Information Disclosure Statement

5. The information disclosure statement submitted on 07 February 2005 has been considered by the examiner. However, since the Office Action in related US Application No. 10/314,578 is not a true publication with a publication date, it is not fully in compliance with 37 CFR 1.97 and thus, it will not be printed on the face of the patent issuing from this application.

Objections/Rejections Withdrawn

6. The objection to the specification as containing US Application serial numbers whose status has changed and require updating is withdrawn in view of the amendments to the specification.

7. The rejection of claims 23-24 under 35 U.S.C. 112, second paragraph as being indefinite is withdrawn in view of applicant's arguments.
8. The rejection of claims 1, 3, 5, 15-39, 52-54, 77, 85, 88-94, 98 and 107-112 under 35 U.S.C. 112, first paragraph, as not complying with the written description requirement is withdrawn in view of the amendments to the claims.
9. The rejection of claims 3-4, 6-9, 39, 91-92 and 94 under 35 U.S.C. 112, first paragraph, for lack of enablement is withdrawn in view of the cancellation of the claims.
10. The rejection of claim 38 under 35 U.S.C. 112, first paragraph, for lack of enablement is withdrawn in view of the cancellation of the claim.
11. The rejection of claims 1, 3-7, 15-16, 18-19, 21-25, 77, 85, 88-92, 94 and 112 under 35 U.S.C. 102(b) as being anticipated by Liang et al (Journal of Clinical Investigation, 98(5):1119-1129, Sept 1996, Ids reference C99 filed 7/12/04) is withdrawn in view of amendments to the claims.

Response to Arguments

12. The rejection of claims 1, 5, 15-37, 52-54, 77, 85, 88-90, 93, 98 and 107-112 and applied to newly added claims 118-120 under 35 U.S.C. 112, first paragraph, for lack of enablement is maintained.

The response argues with a Wands analysis as it relates to the grounds of rejection presented in the previous Office Action mailed 3/30/05. Applicant summarizes the nature of the invention, the examiner agrees. Applicant summarizes the breadth of the claims and states that the examiner challenges the breadth of immune response

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claimed, the breadth of antigens and antibodies claimed but provides no basis for why such breadth is not enabled. Applicant states that antigen specific immune responses and ADCC were both known and sufficiently developed at the time of filing (e.g., see Weiner reference cited by the examiner). Applicant states that the pending claims relate to stimulation of an immune response and Applicant does not have the burden of demonstrating therapy of disease. This has been fully considered but is not found persuasive. Applicant is reminded that during patent examination, the pending claims must be given their broadest reasonable interpretation consistent with the specification. In re Hyatt, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000) (MPEP 2111). Consistent with this, the claims are directed to a method for stimulating an immune response in a subject comprising administering a T-rich immunostimulatory nucleic acid that is 8-100 nucleotides in length and having the formula 5' X₁X₂TTTTX₁X₂ 3' and wherein the nucleic acid may comprise a plurality of poly T motifs optionally interspersed with CpG motifs, methylated or unmethylated CpG dinucleotides, is free of poly-C sequences, includes poly-A sequence, includes poly-G sequence, is greater than 25% C, is greater than 25% A, is administered with an antibody specific for a cell surface antigen or is administered with an antigen and comprises a backbone modification. Further, newly added claim 118 recites that the administered T-rich immunostimulatory nucleic acid is greater than 60% T. Thus, given their broadest reasonable interpretation consistent with the specification, the claims encompass the administration of literally thousands of different T-rich immunostimulatory nucleic acids species for the treatment and prevention of an infection, allergy, asthma and cancer in a

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subject and in combination with an antibody to just any infectious, pathogenic, cancerous or other cell surface antigen or is administered in combination with just any antigen, including cells, cell extracts, proteins, polypeptides, peptides, polysaccharides, polysaccharide conjugates, peptide and non-peptide mimetics of polysaccharides and other molecules, small molecules, lipid, glycolipids, carbohydrates, viruses, parasites, allergens, cancer antigens, microbial antigens, bacteria and bacterial antigens or as disclosed in the specification "The term antigen broadly includes any type of molecule which is recognized by a host immune system as being foreign." (pg. 67, lines 12-13). The specification beginning at page 62, discloses the administration of T-rich immunostimulatory nucleic acids in a non-rodent subject (i.e., human) for the treatment and prevention of any cancer, any infectious disease, any allergic disease and asthma. Further, when combined with any antibody or antigen, the claims broadly encompass millions of compositions for therapy. As set forth in the rejection in the previous Office Action and discussed further below, there is insufficient evidence or nexus that would lead the skilled artisan to predict that the claimed method of stimulating an immune response in a non-rodent subject effectively treats or prevents infection, allergy, asthma and cancer, requiring undue experimentation to practice the full scope claimed invention.

The level of skill of those in the art is agreed to be high, i.e., that of a PhD scientist. Applicant stresses that the level of skill in the art inversely correlates with the amount of direction and guidance provided by the Applicant. Applicant concludes that

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where the level of skill in the art is high, as in the present technology, the required level of guidance is lowered. This has been fully considered but is not found persuasive.

Applicant is reminded that the “amount of guidance or direction” refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. If little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. See, e.g., *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) (“Nascent technology, however, must be enabled with a specific and useful teaching.” The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee’s instruction (see MPEP 2164.03). In the instant case, there is very little known about T-rich immunostimulatory nucleic acids as it was a nascent technology at the time of filing and the art is unpredictable, i.e., Vollmer teach a short polythymidine ODN showed background activity; McCluskie teach a polythymidine nucleic acid that did not have an immunostimulatory effect in immunized mice and Jones teach a T-rich nucleic acid lacking CpG as a negative control for testing ODNs *in vivo*. Thus, while the level of skill of those in the art is deemed to be high, in view that little was known about immunostimulatory T-rich nucleic acids and the art evinces that T-rich immunostimulatory nucleic acids were unpredictable and evolving at the time of filing, more guidance and direction is required to enable the claimed invention. It is noted that Applicant acknowledges that T-rich immunostimulatory nucleic acids were a nascent

technology at the time of filing in which applicant states "Applicant agrees as it was the first to document the immunostimulatory capacity of such nucleic acids." (last paragraph of page 13 of the response filed 10/3/05).

Applicant reiterates that the state and level of predictability in the art indicates that CpG motifs impart immunostimulatory properties to nucleic acids and the ability to make and use CpG immunostimulatory oligonucleotides was known at the time of filing. Applicant argues that the in vitro immune responses observed with T-rich nucleic acids parallel those observed with CpG immunostimulatory oligonucleotides and argues that there is a good in vitro to in vivo correlation for CpG oligonucleotides, citing Weiner (of record) and Hartman (of record) for support. Applicant states that the art of Agrawal (of record) is directed solely to CpG nucleic acids and does not contemplate other classes of immunostimulatory nucleic acid. Applicant asserts that the examiner has ignored data in the specification, which evince that T-rich nucleic acids can be immunostimulatory independent of their CpG content. Applicant argues the cited art of Hartman stating that ODN with shorter half-lives can be administered at higher doses in order to observe in vivo effects and it is therefore, possible to stimulate immune responses in vivo using T-rich nucleic acid in the absence of a backbone modification. Applicant again argues the cited art of Vollmer stating that the results of Vollmer are dosage specific and that for every T-rich nucleic acid there is an optimal dose, which may not be reflected in the data of Vollmer. Applicant criticizes the examiner for ignoring data in the specification showing that a thymidine homopolymer that is 18 nucleotides in length activates B cells in vitro (Fig 5, ODN 2196). Applicant is reminded

that T-rich immunostimulatory nucleic acids that are 100% T are indicated as being enabled in the present rejection. In response to the art of McCluskie and Jones, Applicant states that McCluskie used a dose at which the tested CpG nucleic acids were active and that dose may not be optimal for a non-CpG nucleic acid and the same can be said for Jones, i.e., the dose was optimized for CpG nucleic acid. Applicant quotes from the Weiner reference suggesting that the examiner has taken Weiner out of context and Weiner supports that CpG are potent immunostimulatory agents and CpG act on a variety of cell types and preclinical studies using CpG ODN are promising. Applicant states that the immune stimulatory profiles of CpG ODN and T-rich nucleic acids are similar in terms of immune cells activated and cytokines induced and the fact that T-rich nucleic acids may be less immunostimulatory than CpG ODN under some conditions should not prevent extrapolation from CpG to T-rich nucleic acids. In response to these arguments, it is reiterated that applicant's arguments are evidence that considerable additional experimentation would have to be conducted since each of the different T-rich nucleic acids encompassed by the broad claims would have to be optimized individually since as evidenced by the instant specification and in the teachings of the prior art that the T content and the length of the T-rich immunostimulatory nucleic acid are important determinants of its immune stimulatory effect. The amount of guidance and direction provided in the specification is very narrow compared to the wide breadth of the claims (discussed above), the absence of working examples, and T-rich immunostimulatory nucleic acids were highly unpredictable as evidenced by Hartmann, Vollmer, McCluskie, Jones and Weiner and

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the amount of experimentation required to adapt the practice of CpG nucleic acids to T-rich nucleic acids was quite high, especially in light of the record, which included notable examples of the unpredictability of T-rich nucleic acids to be immunostimulatory, i.e., Vollmer teach a short polythymidine ODN showed background activity and McCluskie teach a polythymidine nucleic acid that did not have an immunostimulatory effect in immunized mice and Jones teach a T-rich nucleic acid lacking CpG as a negative control for testing ODNs *in vivo*. Further, although Weiner acknowledges the therapeutic promise of CpG ODNs, Weiner is quick to caution that despite this promise, all CpG ODN are not alike and more needs to be learned about the heterogenous responses that occur based on host organism, cell subset, or CpG ODN sequence and according to Weiner, the clinical effects of CpG ODNs have not yet been explored and "further work with CPG ODN in both the laboratory and the clinic is needed before we can know their true promise as investigational immunological and therapeutic agents." (see page 461). Thus, given the limited knowledge in the art about the immunostimulatory properties of T-rich immunostimulatory nucleic acids, which applicant agrees was a nascent technology at the time of filing (bottom of page 13 of the response filed 10/3/05) and the fact that this technology was evolving at the time of filing, the cautions of Weiner are even more applicable to the presently claimed T-rich immunostimulatory nucleic acids.

Applicant directs the examiner to working examples and guidance presented in the specification, pointing to Table G and figs 4-12, which document the activity of ODNs 2117, 2137, 2130, 5126, 3401, 2183, 2194, 2196 and 5162 in NK cell activation

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and killing, B cell activation, NKT cell activation, monocyte activation and TNF-alpha and IL-6 indication, which correlates at least with a role in adaptive immunity in vivo citing Hartman for support. While similar sets and subsets of immune cells appear to be activated by CpG and T-rich nucleic acids, the specification does not provide any T-rich nucleic acid that is greater than 29 nucleotides in length commensurate in scope with the claims and none of the disclosed T-rich nucleic acids have been assayed for their in vivo immunostimulatory properties. "(A) specification which describes' does not necessarily also enable' one skilled in the art to make or use the claimed invention." See *In re Armbruster*, 512 F.2d 676, 677, 185 USPQ 152, 153 (CCPA 1975).

Applicant argues that the quantity of experimentation needed to make and use the invention in view of the disclosure and the state of the art at the time of filing is not beyond the level of experimentation routinely practiced by persons of ordinary skill in the art. The response states that Genentech, Calgene and National Recovery Technologies are distinguishable from the present case and undue experimentation would not be required to practice the claimed invention. Although the specification teaches how to make the T-rich immunostimulatory nucleic acids defined by the claims, the specification does not teach how to use these nucleic acids without undue experimentation. Applicant states that the instant application recognizes a specific need and provides an actual answer to that need via the detailed disclosure of immunostimulatory nucleic acids and methods of use (and data in support thereof). Again, the specification does not provide any T-rich nucleic acid that is greater than 29 nucleotides in length, nor many of the T-rich immunostimulatory chemical species

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defined by the claims and none of the disclosed T-rich nucleic acids have been assayed for their in vivo immunostimulatory properties. Applicant leaves this part of their invention to the public to essentially figure out for themselves what the T-rich immunostimulatory nucleic acids look like and which ones effectively treat and prevent infection, allergy, asthma and cancer. This does not constitute adequate enablement. Considering the breadth of the claims, the lack working examples and lack of guidance and direction in the specification, one of skill in the art would be required to perform significant additional experimentation in order to be able to effectively use the invention to the full scope of the claims with a reasonable expectation of success. For instance, one of skill in the art would have to synthesize and screen millions of T-rich immunostimulatory nucleic acids that are 8-100 nucleotides in length in length and having the formula 5' X₁X₂TTTTX₁X₂ 3' and wherein the nucleic acid may comprise a plurality of poly T motifs optionally interspersed with CpG motifs, methylated or unmethylated CpG dinucleotides, is free of poly-C sequences, includes poly-A sequence, includes poly-G sequence, is greater than 25% C, is greater than 25% A, is administered with an antibody specific for a cell surface antigen or is administered with an antigen and comprises a backbone modification or lack a backbone modification as embraced by the claims (particularly the base claims) for immune stimulatory properties, then test for in vivo immune stimulation to determine if a correlation exists between the in vitro and in vivo properties for each of the T-rich nucleic acids and in view of the teachings in the specification as well as in the prior art, indicating that the length and content of the T-rich nucleic acids are important determinants of its immune stimulatory

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effect, one of skill in the art would have to optimize each T-rich nucleic acid individually in view of the evidence of record and applicant's remarks. This amount of additional experimentation is deemed to be undue because in order to practice the full scope of the claimed invention with a reasonable expectation of success, one of skill in the art would have to show evidence overcoming art recognized problems that the broadly claimed T-rich nucleic acids effectively induce an immune response in a subject. By its own terms the instant application describes methods for "screening" and "evaluating" the effect of various T-rich immunostimulatory nucleic acids for treating and preventing an infection, allergy, asthma and cancer in a non-rodent subject (i.e., human). Again, "Nascent technology, however, must be enabled with a specific and useful teaching." *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004).

Therefore, the rejection for lack of enablement is maintained.

New Grounds of Rejections

13. Claim 15 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claims, or amend the claims to place the claims in proper dependent form, or rewrite the claims in independent form. Claim 15 does not further limit base claim 1 because certain species defined by claim 15 fall outside of the genus defined in claim 1. For example, if the T-rich immunostimulatory nucleic acid is 8 nucleotides in length, the maximum T content would only be 75% as X_1X_2 and X_3X_4 are

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presently defined in claim 1, i.e., at most 6 of the 8 nucleotides are T. Only T-rich immunostimulatory nucleic acids that are at least 11 nucleotides in length and wherein the additional nucleotides are T's are greater than 80% T. Thus, dependent claim 15 does not include every limitation of the claim on which it depends and is not a proper dependent claim, i.e., does not further limit the subject matter of claim 1.

14. Claim 120 is rejected under 35 U.S.C. 102(b) as being anticipated by Jones et al (Vaccine 17(23-24):3065-3071, August 6, 1999, cited on PTO-892 mailed 6/29/04).

The claim is drawn to a method of stimulating an immune response in a non-rodent subject comprising administering a T-rich immunostimulatory nucleic acid comprising 5' X₁X₂TTTTX₃X₄ 3' wherein X₁X₂ is methylated CG and wherein X₃X₄ is GT and the immunostimulatory nucleic acid is 8-100 nucleotides in length.

Jones et al teach a method of stimulating an immune response in a monkey comprising administering the T-rich immunostimulatory nucleic acid 2006 having the sequence 5' TCGTCGTTTTGTCTTTTGTCGTT 3', wherein the CG motifs are unmethylated (see entire document, particularly pg. 3066, right column and pg. 3068).

Thus, Jones et al anticipate the claim.

15. Claims 113-117 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter, which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

The response filed 10/3/2005 has introduced NEW MATTER into the claims. Newly added claims 113-117 are directed to methods of administering a T-rich immunostimulatory nucleic acid that is 100% T. The response pointed to claim 1 as filed and pages 4, 11, 135-136 and 133 of the as filed specification for support. A review of the relevant disclosure as pointed to by applicant does not provide adequate written support for the presently claimed subject matter. Claim 1 as originally filed is generic to a Pyrimidine rich immunostimulatory nucleic acid, which could be T or C and not necessarily 100% T. Page 4 of the as filed specification discloses T-rich nucleic acids having various length limitations, however, there is no indication that the T-rich nucleic acid is 100% T. The as filed specification at pages 135-136 and 133 discloses a few T-rich nucleic acids that are 100% T (i.e., SEQ ID Nos:911, 913 and 1094), however, it cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See *In re Smith* 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05. Newly added claims 113-117 now recite limitations, which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in newly added claims 113-117, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C 112. Applicant is required to provide sufficient written support for the limitations recited in

newly added claims 113-117 in the specification or claims, as filed, or remove these limitations from the claims in response to this Office Action.

Conclusion

16. No claim is allowed.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at

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(571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827



LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER